SM.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,027	09/06/2000	Kiyoshi Tanabe	2000_0973A	6651

7590 03/25/2004

Wenderoth Lind & Ponack
2033 K Street NW Suite 800
Washington, DC 20006

EXAMINER	
VOGEL, NANCY S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,027	TANABE ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 23-27 are pending in the case.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/2/04 has been entered.

Claim Objections

It is noted that the last submitted claim is apparently mistakenly numbered as Claim 29. Since there are no submitted claims 27 and 28, it is assumed that Claim 29 should read Claim 27. The claims will be referred to as claim 27. Correction is required.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fijalkowska et al. and Lin et a1., in view of either Imamoto et al. or Iwaki et al. and further in view of Pan et al. (1996 Antimicrobial Agents and Chemotherapy 40:2321-2326) for the reasons of record in Office Action mailed 27 February 2001 and in the Office Action mailed 6 August 2002.

Applicants arguments filed 11/7/03 have been fully considered but they are not deemed to be persuasive.

To recapitulate, Fijalkowska et al. teach a method of mutagenesis by using a mutator gene in a mismatch repair gene group so that more mutations are introduced into one strand of genomic DNA than another, and Fijalkowska et al. teach mutant cells. Fijalkowska et al. do not teach a selection load or isolation of a mutated gene.

Lin et al. teach a mutagenesis method using a mutator gene in a mismatch repair gene group, which inherently introduces more mutations into one strand of genomic DNA than another; see above. Lin et al. do not teach a certain condition for the mutator gene or a selection load condition.

Iwaki et al. teach that dnaQ49 is a temperature-sensitive mutation that increases the frequency of mutations. Iwaki et el do not teach mutagenesis of genomic DNA.

Pan et al. teach ciprofloxacin-resistant mutants of Streptococcus pneumoniae that were generated by stepwise selection at increasing drug concentrations; the mutations are in genomic DNA. Pan et al. teach mutant cells or organism individuals. Different concentrations of drug were tested at each step, and some "fourth-step" mutants were isolated with the same selection load (drug concentration) as the third-

step mutants (see page 2322, right column, and page 2327). Pan et al. also teach that mutants from mutagenesis methods where the steps were repeated had resistance to higher levels of the ciprofloxacin and had more mutations, and that there are primary and secondary target genes for mutations that lead to resistance (see summary in Abstract). Pan et al. note that the presence of mutations in different targets has implications regarding chemotherapy and approaches to minimize the emergence of clinical resistance (see page 2325, right column). Pan et al. also review isolated mutated genes that they had studied previously that caused resistance to ciprofloxacin (page 2321, right column). Pan et al. do not teach the use of mutator genes, but since the mutations are apparently spontaneous mutations, it is reasonable that at least some of them were due to mutations in replication, which, as discussed above, inherently introduces more mutations into one strand than another. Pan et al. also do not teach a certain condition for the mutator gene, such as temperature-sensitivity.

At the time of the invention of the instant application, one of ordinary skill in the art would have been motivated to perform mutagenesis to isolate mutant cells and mutated genes to study the function of the mutated genes for various purposes, such as identifying what genes can be targets for antibiotics, since such studies have clinical implications. Other studies would also have benefited from mutagenesis to identify genes important in other cellular processes. It would have been obvious to use a mutator gene to increase the frequency of mutations to expedite the studies, as taught by Lin et al., and it would have been obvious to use a mutator gene that caused a high frequency of mutations only under a certain condition, such as the dnaQ49 mutation

reviewed by Iwaki et al, in order to have minimized excessive mutations that could have lead to cell death, or that could have complicated studies of a particular mutation. It would also have been obvious to the ordinary artisan to have used a selection load and to have repeated the mutagenesis steps using increasing selection loads as taught by Pan et al. Routine experimentation would have dictated exactly what selection loads at each step would have been optimal, for example, for isolating mutants with increased resistance to an antibiotic based on the cells growth in the presence of the antibiotic at the previous step.

Pan et al. teach some steps in which the increased selection load was not identical to that of the previous step, and other steps in which the selection load was the same as that of the previous step, although the optimization was not exhaustive in the case of Pan et al. Since growth under the selection load condition would have allowed for more mutations to occur with a mutator gene, and since too many mutations would have complicated the studies or have been deleterious, it would have been obvious to remove cells from the certain condition in which mutations were introduced before placing the cells in the new selection load condition. Success would have been expected.

Applicants have argued in their Remarks submitted 11/7/03 that the references do not disclose repetition of the steps of selection of high resistance microorganisms until the tolerance is 1000 times higher than wild type. While this specific level is not disclosed in the reference, the repetition of the steps of selection is taught in Pan et al., it is maintained that the specific level of 1000 fold increase would have been reached by

following the guidance in the references. Therefore, applicants' arguments are not found convincing regarding a specific level of resistance. Applicant further argues that step (b) is repeated under a higher concentration drug than in the prior step (b), and step (a) is repeated under the same concentration of the drug as in step (b) immediately therebefore. However, Pan et al. does disclose the growth of the microorganism under increasing conditions of antibiotics. It is agreed that the step of mutagenesis (a) is not disclosed in Pan et al.; however, the teaching of Fijalkowska et al., Lin et al. and Iwaki et al. of mutagenesis using a mutator gene under a first condition, to result in ability to grow in a second condition, provides the teaching and motivation to conduct the mutagenesis step under a first, or original condition prior to selection. Therefore, it is maintained that the references fairly teach the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 6:30 - 3:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ntv
3/16/04

TERRY MCKELVEY
PRIMARY EXAMINER